PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Form PCT/IPEA/416
3922PTWO/AG/a		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP2004/050962	28.05.2004	30.05.2003
International Patent Classification (IPC) or national classification and IPC		
A61K9/16		
Applicant		
EURAND S.P.A.		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 8 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☒ *sent to the applicant and to the International Bureau)* a total of 4 sheets, as follows:
      ☐ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☒ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the opinion
☐	Box No. II	Priority
☐	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☐	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
15.06.2005	06.09.2005
Name and mailing address of the international preliminary examining authority:	Authorized Officer
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INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/EP2004/050962

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3 and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4)
   - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

Description, Pages	
1-15	as originally filed
Claims, Numbers	
1-32	filed with telefax on 15.06.2005
Drawings, Sheets	
1-3	as originally filed

☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☒ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☒ the claims, Nos. 1,4,9,15,22
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-14,22-26,28, 30
	No:	Claims	15-21,27, 29, 31, 32
Inventive step (IS)	Yes:	Claims	5-7,10,13
	No:	Claims	1-4,8-9, 11, 12,14-32
Industrial applicability (IA)	Yes:	Claims	1-32
	No:	Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

I. Re Item I

Basis of the report

1 This report has been established as if the following amendments of claims had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c) PCT):

1.1 In claim 1 the process of applying a polymeric membrane carried out by coacervation by means of phase separation has been amended from essential feature to an optional feature. The application does not provide a basis for a method of preparing microcapsules other than involving a process of coacervation by means of phase separation.

1.2 Amended claims 4 and 22 refer to a "water-soluble active ingredient".

1.3 Amended claims 9 and 15 refer to a "water-insoluble active ingredient".

V. Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

2 Reference is made to the following documents:

D1 : FR 2 758 461 A (PHARMA PASS) 24 July 1998 (1998-07-24)
D2 : DE 199 30 795 A (ENCAPBIOSYSTEMS) 11 January 2001 (2001-01-11)
D3 : US 2002/064563 A1 (GIBBS IRWIN S ET AL) 30 May 2002 (2002-05-30)
D4 : WO 98/00116 A (SCHERING CORP) 8 January 1998 (1998-01-08)
D5 : US 5 252 337 A (POWELL ET AL) 12 October 1993 (1993-10-12)
D6 : DATABASE WPI Section Ch, Week 198730 Derwent Publications Ltd., London, GB; Class A96, AN 1987-209277 XP002267560 &; JP 62 135419 A (IKEDA MOHANDO) 18 June 1987 (1987-06-18)
D7 : EP 0 706 794 A (JAPAN ENERGY CORPORATION) 17 April 1996 (1996-04-17)
D8 : EP 0 475 536 A (TAKEDA) 18 March 1992 (1992-03-18)

3 INDEPENDENT CLAIM 1

3.1 The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claim 1 is not inventive in the sense of Article 3332) PCT.
Document D3 is considered as being the closest prior art and discloses (the references in parentheses applying to this document):
Sugar beads coated with a solution comprising topiramate and povidone. Although fluidized bed granulation is preferred, also coazervation as coating technique is envisaged (example 1; paragraph 44). A taste masking coating of cellulose acetate is provided (example 2). The difference between the subject-matter of claim 1 and D3 is that claim 1 refers to a method involving coazervation by means of phase separation.
The problem to be solved is the provision of microcapsules having an active ingredient in a polymeric membrane. The solution provided is a method comprising a process involving coacervation by means of phase separation.
This solution however cannot be considered as involving an inventive step (Art. 33(3) PCT), for the following reasons: D3 refers to coacervation as coating technique. Phase separation is a well-established method for the preparation of microcapsules, known to the person skilled in the art. In the absence of further technical features characterising the coacervation method by phase separation, the choice of the phase separation method as such is considered to be a matter of normal experimental design.

3.2 Document D2 discloses particles comprising a core of sodium alginate (500 micrometer) and a coating of estradiol and polylactic acid. Hardening takes place by contact with calcium chloride solution (example 1). The active ingredient is embedded within the calcium alginate matrix. D2 does therefore not anticipate the novelty of claim 1.

4 INDEPENDENT CLAIM 15

4.1 The application does not provide any physical evidence supporting the claimed and desired concentration gradient of the drug in the polymeric membrane. In the absence of such evidence, the claimed gradient has be seen as a mere result to be achieved, a desideratum, that can not serve as distinguishing technical feature vis-à-vis the prior art.

4.2 The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claim 15 is not new in the sense of Article 33(2) PCT.
Document D1 discloses (the references in parentheses applying to this document):
Composition comprising an inert substrate (50-500 µm) (fenofibrate) and a coating of micronised drug (< 10 µm) in a hydrophilic polymer (polyvinylpyrrolidone). The coating suspension comprises furthermore sodium laurylsulfate (example 1).

4.3 The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claim 15 is not new in the sense of Article 33(2) PCT.
Document D3 discloses (the references in parentheses applying to this document):
Sugar beads coated with a solution comprising topiramate and povidone. Although fluidized bed granulation is preferred, also coazervation is envisaged as coating technique is envisaged (example 1; paragraph 44). A taste masking coating of cellulose acetate is provided (example 2).

4.4 The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claim 15 is not new in the sense of Article 33(2) PCT.
Document D4 discloses (the references in parentheses applying to this document):
Sugar spheres coated with a suspension comprising hydroxymethylpropylcellulose, a micronised drug and simethicone (examples 1,2,5). The polymer may also be gelatine (page 5, line 6). Hydroxymethylpropylcellulose is soluble in water at temperatures below 60 °C and can therefore be considered as a water-soluble polymer.

4.5 The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claim 15 is not new in the sense of Article 33(2) PCT.
Document D5 discloses (the references in parentheses applying to this document):
Verapamil dispersed in a solution comprising PVP is sprayed on non-pareil seeds (ex. 1).

4.6 The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claim 15 is not new in the sense of Article 33(2) PCT.
Document D6 discloses (the references in parentheses applying to this document):
Granules comprising sucrose cores (100-3000 µm) and a coating of diclofenac salts

dispersed in a polymer such as polyvinylpyrrolidon.

4.7 The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claim 15 is not new in the sense of Article 33(2) PCT.
Document D7 discloses (the references in parentheses applying to this document):
Particles comprising core particles (100-700 µm) and a coating of a drug and HPMC (cl. 1-5,8; ex. 1-4).

4.8 The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claim 15 is not new in the sense of Article 33(2) PCT.
Document D8 discloses (the references in parentheses applying to this document):
Spherical granules having a core (14-80 mesh = 177-1410 µm) and a coating of a drug and HPMC, also containing magnesium or calcium carbonate.

5 INDEPENDENT CLAIM 22

5.1 The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claim 22 is not inventive in the sense of Article 33(3) PCT.
Document D6 discloses (the references in parentheses applying to this document):
Granules comprising sucrose cores (100-3000 µm) and a coating of diclofenac salts dispersed in a polymer such as ethylcellulose or HPMC phthalate. Claim 22 differs from D6 in the amount of polymer. The problem to be solved is considered to be the provision of alternative microcapsules. The solution provided in claim 22 is however considered not to involve an inventive step (Article 33(3) PCT), as in the absence of a surprising technical effect, the choice of amount of the polymer is considered to be a matter of normal experimental design.

6 DEPENDENT CLAIMS 2-4, 8-12, 14, 16-20, 22-30
Dependent claims 2-4, 8-12, 14, 16-20, 25-30 do not contain any features which, in combination with the features of any claim to which they refer, meet the requirements of the PCT in respect of novelty and/or inventive step (Article 33(2) and (3) PCT).

7 DEPENDENT CLAIMS 5-7, 10, 13

The combination of the features of dependent claims 5-7, 10, 13 are neither known from, nor rendered obvious by, the available prior art. The reasons are as follows: The prior art does not disclose a method of preparing microcapsules involving a coacervation by means of phase separation, having a membrane of ethylcellulose comprising drug particles, the method involving a coacervation by means of phase separation.

VIII. Re Item VIII
Certain observations on the international application

8 Claims 15 and 22 are not supported by the description as required by Article 6 PCT.

8.1 Claims 15 and 22 are not supported by the description as required by Article 6 PCT, as their scope is broader than justified by the description. The reasons therefor are the following: The description provides support only for microcapsules obtainable by the method of coacervation by phase separation. No support is provided for any composition having the technical features as defined in claims 15 and 22. Hence, claims 15 and 22 are not supported by the description as required by Article 6 PCT.

EPO - DG 1

20. 06. 2005

(93)

AMENDED CLAIMS

1. Method of preparing microcapsules having a core with dimensions ranging from 50 to 1200 μm and a polymeric membrane containing at least one active ingredient and, optionally, at least one membrane additive characterised in that the application of said polymeric membrane to said core is carried our by a process of coacervation by means of phase separation of a suspension of said active ingredient and, optionally, of said membrane additive in a solution of a water-soluble or a water-insoluble coating polymer.

2. Method as claimed in claim 1 comprising the following steps:

(a) forming a solution of said coating polymer in an aqueous or in organic solvent;

(b) suspending the cores, the particles of active ingredient and, optionally, any membrane additive in the solution obtained in (a),

(c) causing coacervation of the coating polymer in the suspension obtained in (b) by means of phase separation,

(d) optionally, subjecting the microcapsules to a hardening treatment of the membrane.

(e) recovering the microcapsules thereby obtained.

3. Method as claimed in claim 2 wherein step a) and b) are carried out as a single step.

4. Method as claimed in claims 1 to 3, wherein said coating polymer is a water insoluble polymer, the solution of said polymer is in an organic solvent and said active ingredient is water-soluble.

5. Method as claimed in claim 4 wherein said polymer is ethylcellulose.

6. Method as claimed in claim 4 or 5 wherein the solvent used in step a) is cyclohexane.

7. Method as claimed in claim 4 to 6 wherein the additive added in step b) is selected from lactose, mannitol, polyvinylpyrrolidone, hydroxypropylmethylcellulose, methylcellulose, hydroxypropylcellulose, swelling agents such as sodium carboxymethylamide, croscarmellose, crospovidone, pregelatinized starch and pH modifiers.

8. Method as claimed in claims 4 to 7, wherein in step c) phase separation takes place by variation in temperature.

9. Method as claimed in claims 1 to 3, wherein said coating polymer is a water soluble polymer, the solution of said polymer is in an aqueous solvent and said active ingredient is water-insoluble.

10. Method as claimed in claim 9 wherein said polymer is selected from the group consisting of gelatine, cellulose acetate phthalate, hydroxypropylmethylcellulose phthalate or derivates thereof.

11. Method as claimed in claim 9 or 10, wherein the solvent used in step a) is water at a pH comprised between 1 and 9.

12. Method as claimed in claim 11, wherein the pH is comprised between 4 and 7.

13. Method as claimed in claims 9 to 12, wherein the additive added in step b) is selected from dibasic calcium phosphate, calcium sulphate, barium sulphate, calcium carbonate, magnesium carbonate and silicates.

14. Method as claimed in claim 9 to 13, wherein in step c) phase separation takes place by pH variation, variation in temperature or insolubilisation of the polymer by adding phase-separation inducing agents.

15. Microcapsules comprising a core having dimension ranging from 50 to 1200 µm and a polymeric membrane coating said core based on a water-soluble coating polymer and containing at least one water-insoluble active ingredient dispersed therein in the form of solid particles, said particles being dispersed inside said polymeric membrane with a concentration that decreases progressively moving from the core towards the distal part of the membrane.

16. Microcapsules as claimed in claim 15, obtainable by a method as claimed in claims 4 to 8.

17. Microcapsules as claimed in claims 15 and 16 wherein the taste of the active principle is masked.

18. Microcapsules as claimed in claims 15 to 17 characterised by a modified release of the active principle.

19. Microcapsules as claimed in claim 18 wherein said modified release is a delayed release.

20. Microcapsules as claimed in claims 15 to 19, wherein the water-soluble polymer is chosen from gelatine, cellulose acetate phthalate, hydroxypropylmethylcellulose phthalate and derivates thereof.

21. Microcapsule as claimed in claims 15 to 20, wherein said polymeric membrane further contains water-insoluble membrane additives.

22. Microcapsules comprising a core having dimension ranging from 50 to 1200 µm and a polymeric membrane coating said core based on a water-insoluble coating polymer and containing at least one water-soluble active ingredient homogeneously dispersed therein in the form of solid particles, said water-insoluble coating polymer being present in amounts ranging from 2% to 40% and said active principle being present in amounts ranging from 01% to 40%, with respect to the weight of the microcapsule.

23. Microcapsules as claimed in claim 22 obtainable with the method claimed in claims 9 to 14.

24. Microcapsules as claimed in claims 22 or 23 characterised by a modified release of the active ingredient.

25. Microcapsules as claimed in claims 22 to 24, wherein the water-insoluble polymer is selected from ethylcellulose and its derivates.

26. Microcapsules as claimed in claims 22 to 25, wherein the polymeric membrane contains water-soluble additives.

27. Microcapsules as claimed in claims 15 to 26, wherein the active ingredient has dimensions ranging from 0.1 to 80 µm.

28. Microcapsules as claimed in claim 27, wherein the active ingredient has dimensions ranging from 1 to 30 µm, and ranges from 0.2 to 21% by weight of the microcapsules.

29. Microcapsules as claimed in claims 15 to 28, wherein the core constitutes 50% to 95% by weight of the microcapsules and the coating polymer varies from 2 to 20% by weight of the microcapsule.

30. Microcapsules as claimed in claims 15 to 29, wherein the membrane contains additives having a mean diameter ranging from 0.1 to 80 µm and constituting from 2 to 10% by weight of the microcapsule.

31. Microcapsules as claimed in claim 30, wherein the membrane additives have a mean diameter ranging from 7 to 30 µm and constitute from 3% to 5% by weight of the microcapsule.

32. Microcapsules as claimed in claims 15 to 31 coated with a further coating layer.